Chemical and Biological Oxidation of Organohalides. Peracid Oxidation of Alkyl Iodides

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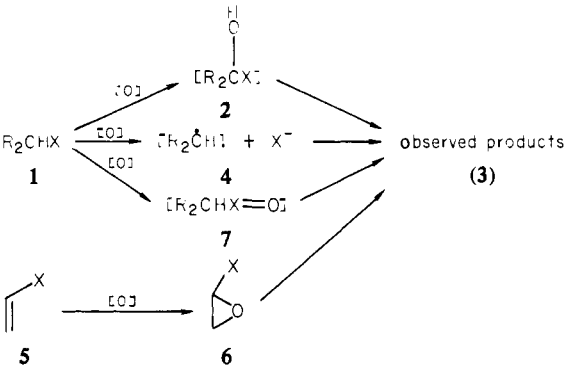
Abstract: The peracid oxidation of seven alkyl iodides has been examined in nonpolar solvents. The stoichiometry for the reaction is shown to be $(8 + n)ArCO_3H + 6RI + 3H_2O \rightarrow (8 + n)ArCO_2H + 6ROH + 2I_2 + I_2O_5 + (n/2)O_2$ (R = *n*-heptyl, Ar = *m*-ClC_6H_4, n = 4–16). Evidence is presented for the intermediacy of an alkyliodosyl compound in these oxidations. Primary alkyl iodides give exclusively displacement products, whereas secondary iodides give a mixture of products resulting from displacement, elimination, and α-carbon oxidation. Tertiary iodides give products resulting from displacement and elimination. Mechanisms for the formation of these products are presented. The overall rate of peracid mediated reaction is dependent upon the alkyl group: tertiary > secondary > methyl ≳ primary iodides. The bioactivation of organohalides via an analogous halogen oxidation process is discussed.

Organohalides are widely used in commerce, industry, and medicine. Many of the compounds in this class are recognized as being toxic or carcinogenic.[1] Many organohalides are potent alkylating agents, and their toxic or carcinogenic effect may be attributed to this. However, a number of toxicologically interesting compounds require bioactivation. This activation process in many cases requires metabolism by cytochrome P-450 mixed-function oxidase enzymes.[2,3] Numerous mechanisms for the bioactivation of organohalides have been proposed including oxidation of the halogen-bound carbon via carbon–hydrogen bond oxygen insertion (e.g., **1** → **2**), reduction of the carbon–halogen bond generating a carbon-centered free radical and halide ion (e.g., **1** → **4**), and oxidation of carbon–carbon double bonds in unsaturated organohalides via epoxidation (e.g., **5** → **6**).[2,3] We recently suggested that an additional, important mechanism for the bioactivation of many organohalides may be direct halogen oxidation to a hypervalent state[3] (e.g., **1** → **7**). The subsequent, nonenzymic chemistry of the intermediate hypervalent organohalogen species may account for the toxicological properties of many organohalides which require activation (**1** → **7** → **3**). It has been proposed that an iron-bound carbene-like oxene is involved in the oxygen-transfer process mediated by cytochrome P-450 enzymes[2d,4] and that peracids are chemical "oxenoid-transfer" mimics of these enzymes.[2d,5] In view of this mechanism, an organohalogen oxide **7** is attractive as the hypervalent organohalogen species. Recently, several groups have reported on the synthetic utility of hypervalent organoiodides generated through peracid oxidation.[6,7] These researchers propose that reactive alkyliodosyl compounds (**7**, X = I) are involved as intermediates leading to the observed products. The aryl counterparts of these proposed species are well-known.[8] In order for halogen oxidation to be considered as a major metabolic route for organohalogen compounds, the chemistry of the hypervalent organohalide intermediate must be consistent with the observed biotransformations of the precursor organohalogen compound and model the enzymic process. Thus, we have undertaken a detailed study of the chemistry of hypervalent organoiodide species generated via peracid oxidation as the initial phase of an investigation to determine the importance of metabolic halogen oxidation of organohalides in vivo.

Scheme I. Postulated Mechanisms of Haloalkane Metabolism by Cytochrome P-450



Results and Discussion

The Nature of the Hypervalent Organoiodide Intermediate. Alkyliodosyl species have been postulated to be the synthetically useful intermediates derived from peracid oxidation of alkyl iodides.[6b] The intermediacy of these compounds has not been established nor has the stoichiometry of the oxidation reaction been determined. The molar ratio of peracid to iodide used ranges from 1.5 to 2.2.[6] We have established that for the *m*-chloroperoxybenzoic acid (*m*-CPBA) oxidation of *n*-heptyl iodide, a representative substrate which undergoes a single reaction process (displacement), approximately 2.0 mol of peracid/mol of alkyl iodide are required for consistently complete reaction. Complete reaction with slightly less peracid (1.8–1.9 mol) was occasionally observed, but conversion percentages were erratic at these ratios of peracid to iodide.

The requirement for 2 molar equiv of peracid suggests the possible intermediacy of an iodyl or other iodine (3+) species. Stable aryliodyl compounds are rapidly and cleanly generated from

(1) (a) Heidelberger, C. *Annu. Rev. Biochem.* **1975**, *44*, 29. (b) Fishbein, L. *Sci. Total. Environ.* **1979**, *11*, 111, 163. (c) *Mutat. Res.* **1976**, *32*, 267. (d) Weisburger, E. *EHP, Environ. Health Perspec.* **1977**, *21*, 7.

(2) (a) Van Dyke, R. *EHP, Environ. Health Perspec.* **1977**, *21*, 121. (b) Van Duuren, B. L. *Ibid.* **1977**, *21*, 17. (c) Stevens, J. L.; Anders, M. W. *Biochem. Pharmacol.* **1979**, *28*, 3189. (d) Ullrich, V. *Top. Curr. Chem.* **1979**, *83*, 67.

(3) Guengerich, F. P.; Crawford, W. M.; Domoradski, J. Y.; Macdonald, T. L.; Watanabe, P. G. *Toxicol. Appl. Pharmacol.* **1980**, *55*, 303.

(4) Hamilton, G. A. In "Molecular Mechanisms of Oxygen Activation"; Hayaishi, O., Ed.; Academic Press: New York, 1974; p 405.

(5) Ullrich, V.; Wolf, J.; Amadori, E.; Standinger, Hj. *Hoppe-Seyler's Z. Physiol. Chem.* **1968**, *349*, 85.

(6) (a) Cambie, R. C.; Lindsay, B. G.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Chem. Commun.* **1978**, 919. (b) Reich, H. J.; Peake, S. L. *J. Am. Chem. Soc.* **1978**, *100*, 4888. (c) Ogata, Y.; Aoki, K. *J. Org. Chem.* **1969**, *34*, 3974, 3978. (d) Cambie, R. C.; Chambers, D.; Lindsay, B. G.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1*, **1980**, 822. (e) Davidson, R. I.; Kropp, P. J. "Abstracts of Papers", 179th National Meeting of the American Chemical Society, Houston, TX, March, 24–28, 1980; American Chemical Society: Washington, DC, 1980; Abstract 41.

(7) For related chemical oxidation of organoiodides see: (a) Carraway, J.; Donovan, R. J. *J. Chem. Soc., Chem. Commun.* **1979**, 1108; (b) Baum, K.; Beard, C. D. *J. Org. Chem.* **1975**, *40*, 2536; (c) Linskeseder, M.; Zibral, E. *Justus Liebigs Ann. Chem.* **1977**, 1039.

(8) (a) Banks, D. F. *Chem. Rev.* **1966**, *66*, 243. (b) See also: Koser, G.-F.; Wettach, R. H. *J. Org. Chem.* **1980**, 45, 1542.

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aryl iodides by oxidation with 2 equiv of peracid. Alternatively, an iodosyl or other iodine (1+) intermediate could be the reactive species, and further consumption of peracid via iodine (1+) oxidation or alternate process then occurs rapidly after displacement.

Oxidant titration and spectroscopic determination of elemental iodine content of the reaction mixture obtained after complete alkyl iodide oxidation revealed that of the initial oxidation equivalents one-third was lost as a volatile oxidant, presumably molecular oxygen, and that iodine (I_2) and iodine pentoxide (I_2O_5) were the iodine-containing products. These products were present in a 2:1 molar ratio. The 2:1 ratio of iodine to iodine pentoxide was constant over a range of peracid to substrate ratios from 1:1 (incomplete alkyl iodide oxidation) to 4:1 (greater than twice the theoretical requirement for alkyl iodide oxidation). These data are consistent with the stoichiometry of the heptyl iodide oxidation by *m*-CPBA being as summarized in eq 1.

$$12m\text{-CPBA} + 6RI + 3H_2O \rightarrow 12m\text{-CBA} + 6ROH + 2I_2 + I_2O_5 + 2O_2 \quad (1)$$

R = *n*-heptyl

Iodine pentoxide, which has been previously observed in the oxidation of alkyl iodides with Cl_2O_7,[7b] does not arise from peracid oxidation of elemental iodine. The iodine to iodine pentoxide ratio does not change even with a large excess of peracid present (vide supra), and in control experiments less than a 15% loss of peracid-oxidizing equivalents and a 5% reduction of elemental iodine content were observed when the two were mixed over greater than three normal reaction periods (30 min). Thus, the formation of iodine pentoxide during the oxidation of *n*-heptyl iodide offers the most compelling proof to date of an intermediate oxygenated iodine species in the peracid oxidation of alkyl iodides.

We believe that the constant ratio of iodine to iodine pentoxide is a consequence of the well-established disproportionation of hypoiodite to iodide and iodate (eq 2).[9] Subsequent peracid

$$\begin{array}{ccccc} 3IO^- & \rightarrow & 2I^- & + & IO_3^- \\ & & \downarrow{\scriptstyle [O]} & & \downarrow{\scriptstyle +H^+,\ -\frac{1}{2}H_2O} \\ & & I_2 & & \frac{1}{2}I_2O_5 \end{array} \quad (2)$$

oxidation of iodide to elemental iodine and dehydration of iodic acid would afford the iodine-containing products in the observed ratios. This sequence of reactions for the formation of iodine and iodine pentoxide is well precedented and yields thermodynamically stable iodine oxidation states under these oxidizing conditions.[9]

The average oxidation state of iodine in $[2I_2 + I_2O_5]$ is +1.67 and would theoretically require a 1.33:1.0 molar ratio of peracid to alkyl iodide for complete oxidation. We have been unable to establish this ratio (1.33:1.0) as the minimum peracid oxidation requirement, however. We believe that an agent is generated during the course of the reaction which is capable of catalytically decomposing peracid to carboxylic acid and oxygen. We have established that peracid decomposition does indeed occur after complete consumption of alkyl iodide and achievement of a stable iodine to iodine pentoxide ratio when exess peracid (greater than 2:1 molar ratio) is employed. Catalytic destruction of peracid would cause the 2:1 molar ratio employed here not to be a fundamental requirement for oxidation of alkyl iodides by peracids and would obviate the need to propose disproportionation of an iodine (3+) species. In addition, simple disproportionation of IO_2^- would lead to a 2:3 molar ratio of elemental iodine to iodine pentoxide and not the 2:1 ratio observed.

Hypohalite ion (IO^-) or its corresponding acid in our postulated scheme is derived from alkyl iodide oxidation and subsequent nucleophilic displacement (S_N1 or S_N2) on an alkyliodosyl species (vide infra). Previous workers have noted the hyperelectrophilicity of the hypervalent iodide intermediates generated via this process.[6b]

(9) Cotton, F. A.; Wilkinson, G. "Advanced Inorganic Chemistry. A Comprehensive Text", 3rd ed.; Wiley-Interscience: New York, 1972; pp 458–489.

Scheme II. Proposed Reaction Sequence for Peracid Oxidation of Alkyl Iodides

$$6RI + 6ArCO_3H \rightarrow 6ArCO_2H + 6[\overset{+}{R}\overset{-}{IO}] \quad (I)$$

$$6[\overset{+}{R}\overset{-}{IO}] + 6H_2O \rightarrow 6ROH + 6HOI \quad (II)$$

$$6HOI \rightarrow 4HI + 2HIO_3 \quad (III)$$

$$4HI + 2ArCO_3H \rightarrow 2ArCO_2H + 2I_2 + 2H_2O \quad (IV)$$

$$2HIO_3 \rightarrow I_2O_5 + H_2O \quad (V)$$

$$nArCO_3H \xrightarrow{\text{catalyst}} nArCO_2H + (n/2)O_2 \quad (VI)$$

$$(8+n)ArCO_3H + 6RI + 3H_2O \rightarrow (8+n)ArCO_2H + 6ROH + 2I_2 + I_2O_5 + (n/2)O_2$$

R = *n*-heptyl, Ar = *m*-ClC_6H_4, *n* = 4–16

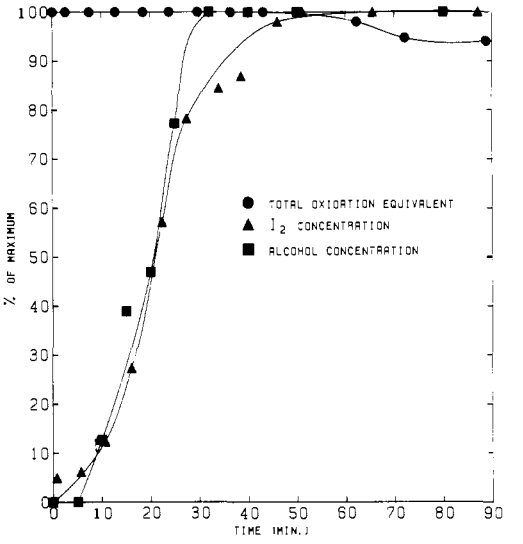
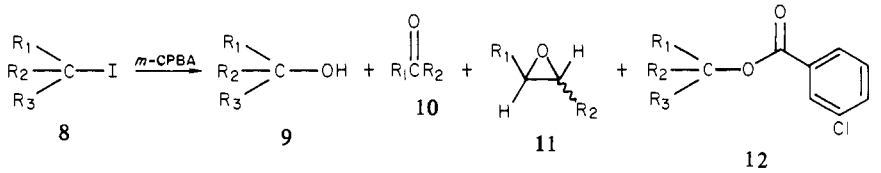


Figure 1. Rates of formation of alcohol and iodine and the disappearance of the total oxidation equivalent for the reaction of *n*-heptyl iodide with *m*-CPBA. Reaction conditions: *n*-heptyl iodide (3.0 mmol); *m*-CPBA (6.0 mmol) in $CDCl_3$ (50 mL) at 0 °C. The total oxidation equivalent decreased to 67% of the maximum value after 2.5 h.

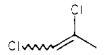
The nucleophile in the present case is water which is present as a contaminant of the peracid. Attempts to rigorously dry the peracid and reaction solvent led to depressed quantities of alcohol (ca. 60%) and enhanced quantities of alkyl benzoate (ca. 40%). This product ratio is close to the minimum alcohol theoretical value since 0.5 mol of water is produced for each mole of alkyl iodide oxidized. Using water-saturated methylene chloride as the reaction solvent completely inhibited alkyl benzoate formation from *n*-heptyl iodide and generated alcohol exclusively. Peresters were not observed as reaction products. Thus, we postulate that the oxidation of *n*-heptyl iodide by *m*-CPBA is summarized by the following sequence and stoichiometry (Scheme II).

The relative rates for the formation of alcohol and iodine products and for the decrease in total oxidation equivalents of the reaction represented in Scheme II are presented in Figure 1. Within experimental error, the rates of alcohol and iodine formation are identical and distinct from the rate of decrease in total oxidant titer. The lack of coincidence in formation of alcohol–iodine and in decrease in total oxidant supports the independent reaction pathways postulated (Scheme II: eq I–IV and VI, respectively). The identity in the rates of alcohol and iodine generation, coupled with the lack of observable alkyl iodosyl intermediates, suggests that alkyl iodide oxidation (eq I) is the rate-determining step in the cascade to the observed products—alcohol and iodine (eq II–IV). This conclusion is consistent with the established extremely rapid rate of disproportionation of hypoiodite at all temperatures (so that it is unknown in solution)[9] (eq III) and the rapid oxidation of iodide ion to iodine under acidic conditions (eq IV). The relative rate of dehydration of iodic acid has not been determined (eq V). This reaction, which presumably

Table I. Product Distribution for the Reaction of Alkyl Iodides 8 with *m*-Chloroperoxybenzoic Acid[a]



8 9 10 11 12

expt no.	substrate R¹	R²	R³	m-CPBA, equiv	conditns solvent	temp, °C (±2)	time, min	products, % (±3) 9	10	11	12
1	n-C_6H_{13}	H	H	2.0	CH_2Cl_2	27	6	90	0	0	10
2[b]	$(H_3C)_3C$	H	H	2.0	CH_2Cl_2	27	8	85	0	0	5
3[c]	H_3C	H_3C	H_3C	2.0	CH_2Cl_2	27	2	85	0	0	15
4	$-(CH_2)_5-$		H	2.0	CH_2Cl_2	27	8	54	14	32	0
5		H	H	2.0	CH_2Cl_2	27	5	100	0	0	0
6	n-C_6H_{13}	H_3C	H	2.0	CH_2Cl_2	40	3	31	29	24	16
7	n-C_6H_{13}	H_3C	H	2.0	CH_2Cl_2	27	8	48	23	20	9
8	n-C_6H_{13}	H_3C	H	2.0	CH_2Cl_2	0	15	52	19	23	6
9	n-C_6H_{13}	H_3C	H	2.0	CH_2Cl_2	−40	35	48	20	22	10
10	n-C_6H_{13}	H_3C	H	2.0	CH_2Cl_2	−80	60	55	18	23	4
11	n-C_6H_{13}	H_3C	H	2.0	$CHCl_3$	0	15	58	19	18	15
12	n-C_6H_{13}	H_3C	H	2.0	$CHCl_3$	61	3	30	26	28	16
13	n-C_6H_{13}	H_3C	H	2.0	C_6H_6	0	15	33	24	25	18
14	n-C_6H_{13}	H_3C	H	2.0	C_6H_6	80	3	28	22	28	22
15	n-C_6H_{13}	H_3C	H	2.0	EtOAc	0	15	65	7	26	2
16	n-C_6H_{13}	H_3C	H	2.0	EtOAc	77	3	46	18	18	18
17	n-C_6H_{13}	H_3C	H	2.0	Et_2O	0	15	52	12	23	13
18	n-C_6H_{13}	H_3C	H	2.0	Et_2O	35	3	45	16	21	18
19	n-C_6H_{13}	H_3C	H	2.0	THF	0	15	55	9	36	0
20	n-C_6H_{13}	H_3C	H	2.0	THF	66	3	67	9	22	2
21	n-C_6H_{13}	H	H	2.0	$CH_2Cl_2(H_2O)$	27	8	100	0	0	0
22	n-C_6H_{13}	H	H	1.5	$CH_2Cl_2(H_2O)$	27	8	100	0	0	0
23	n-C_6H_{13}	H	H	4.0	$CH_2Cl_2(H_2O)$	27	30	100	0	0	0
24[d]	n-C_6H_{13} + n-$C_6H_{13}CH(OH)CH_3$	H	H	2.0	CH_2Cl_2	27	8	87	0	0	13

[a] All data presented represent the average of a minimum of two trials. [b] In experiment 2, *tert*-pentyl (rearranged) derivatives and an unidentified product were obtained (10%). [c] All experiments except the tert-butyl iodide (experiment 3) gave a mass balance of volatile material (Krugelrohr distillation) 80–100% of theoretical and proceeded to complete conversion (except experiment 22). [d] Experiment 24 afforded 10–19% (variable amounts) of 2-octanone when an equimolar mixture of *n*-heptyl iodide and 2-octanol was treated with 2 equiv of *m*-CPBA.

has little impact on the course of the alkyl iodide oxidation–displacement sequence, does not occur under the aqueous reaction conditions (1% water) employed in this rate study.

Reactions of the Hypervalent Organoiodide Species. The hypervalent organoiodide species generated from peracid oxidation of alkyl iodides have been shown to undergo three types of reactions: nucleophilic substitution,[6a] elimination,[6b] and α-carbon oxidation.[6a] We have provided evidence for the formation of alkyl iodosyl compounds via peracid oxidation, although these species may not be the agents undergoing the observed reaction processes. Aryl iodosyl compounds are known to coexist in aqueous or acidic media with their dihydrate or hydroxycarboxylate adducts.[8] Our data cannot exclude intervention of the corresponding alkyl iodosyl adducts in the observed reactions. Regardless of the precise nature of the hypervalent organoiodide intermediate, the type of reaction as determined by product distribution, is dependent on substrate structure and solvent (Table I). All of the solvents examined were nonnucleophilic. When the oxidation is carried out in nucleophilic solvents (e.g., methanol, acetic acid), nucleophilic attack by the solvent is the overwhelming reaction type observed.[6]

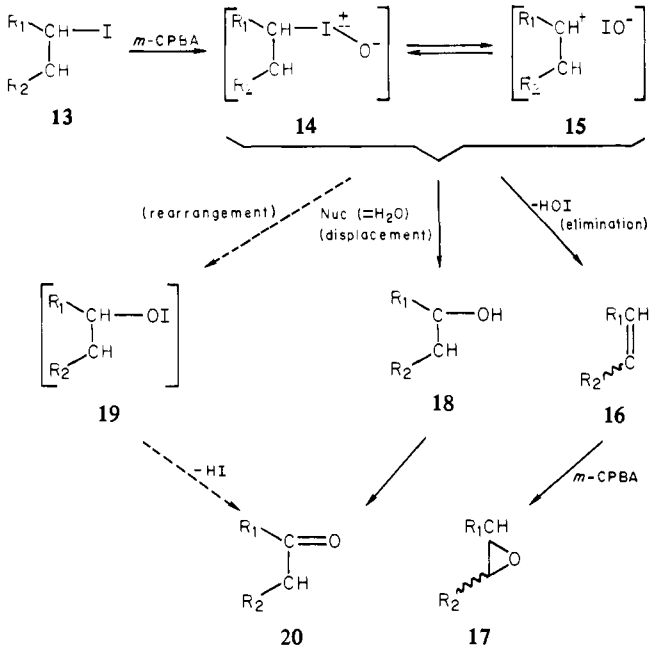
Reaction type was determined primarily by substrate structure under our reaction conditions. Thus, primary iodides gave predominately displacement products (experiments 1, 2, and 5). A carbocationic shift was observed only when substitution at the iodine-bearing carbon is sterically encumbered. Neopentyl iodide oxidation gave only *tert*-pentyl alcohol and *m*-chlorobenzoate resulting from nucleophilic addition to the tertiary carbocation formed by methyl migration. Secondary iodides underwent all three reaction processes depending upon the substrate and reaction conditions (experiments 4 and 6). However, no rearranged products resulting from alkyl migration were observed. Secondary iodides were the only substrates which gave appreciable quantities of α-carbon oxidation (e.g., ketone **10**). Secondary iodides also invariably gave epoxide products which apparently arise from elimination followed by oxidation of the resulting olefin under the reaction conditions. *tert*-Butyl iodide, the only tertiary iodide examined, generated *tert*-butyl alcohol and *tert*-butyl chlorobenzoate. The diminished mass balance observed for this reaction (ca. 60%) could be a consequence of elimination which would form a volatile olefinic or epoxide product.

We have established that the substitution products found in these reactions are due to displacement of the hypervalent iodine species by nucleophiles present in the reaction medium. Thus, the alcohol **9** and *m*-chlorobenzoate **12** products (Table I) result from displacement of the intermediate hypervalent iodide by water and *m*-CBA. Alcohol **9** is observed even under rigorously anhydrous conditions since 0.5 molar equiv of water are produced in the course of the reaction. As previously noted peracid oxidation of alkyl iodides in nucleophilic solvents provides an excellent means for solvolytic displacement. It should be noted that *m*-CBA esters are not observed in polar nucleophilic solvent media. The displacement of primary (*threo*-1,2-dideuterio-1-iodo-3-methyl-3-phenylbutane[10]) and secondary ((*S*)-2-iodooctane[6d,e]) hypervalent organoiodide intermediates proceeds with inversion demonstrating S_N2 characteristics. The formal displacement products of *tert*-butyl iodide and the rearrangement products of neopentyl iodide suggest that an S_N1-type substitution process involving incipient or established carbocationic intermediates can occur.

Formation of epoxide occurs by initial olefin formation via elimination of the hypervalent iodide species and subsequent epoxidation. This elimination process could occur via a pericyclic syn elimination of the iodosyl intermediate[6b] or through carbo-

(10) Reich, H. J., personal communication.

Scheme III. Mechanisms for the Formation of Products from Peracid Oxidation of Alkyl Iodides



13 14 15 19 18 16 20 17

cationic intermediates. The mechanism by which the α-carbon is oxidized to a carbonyl function is less clear.

We have studied the formation of 2-octanone from 2-iodooctane as a representative carbonyl-forming reaction. 2-Octanol was oxidized to the ketone by peracid in the presence of iodine with less than 10% conversion. Oxidation of *n*-heptyl iodide (1.0 equiv) with *m*-CPBA (2.0 equiv) in the presence of 2-octanol (1.0 equiv) in methylene chloride (0 °C) resulted in variable oxidation to 2-octanone (10–19%). The yield of ketone when 2-octyl iodide alone was reacted with peracid in methylene chloride at 0 °C was consistently 19%. The cause for this discrepancy in 2-octanone yields could be the result of kinetic features; e.g., the alcohol and transient oxidizing species (perhaps hypoiodite) are generated in close proximity when the *sec*-alkyl iodide is oxidized. Peracid oxidation of alkyl iodides has been shown to generate a transient "positive iodine" source capable of iodinating unactivated aromatic rings;[7c] such a species may be capable of oxidizing alcohols. Displacement competes with α-carbon oxidation in secondary iodides to a certain extent, since the addition of water to the reaction media increases the formation of secondary alcohol at the expense of ketone (~15%) and benzoate (~0%). Water could be competing simply for the transient oxidizing species, although this rationale would appear less likely because methanol and primary alcohols are not affected by this transient agent. However, carbonyl products are observed even when strongly nucleophilic, anhydrous solvents are employed as reaction media which should effectively compete with water as a nucleophile and inhibit alcohol formation (MeOH, 10%; AcOH, 15%[6a]). Thus, an additional carbonyl-forming process could be considered which does not proceed via the intermediate alcohol. This sequence involves rearrangement of the *sec*-alkyliodosyl compound to an alkyl hypoiodite and elimination of hydrogen iodide from the hypoiodite to generate the carbonyl. The fact that secondary iodides, and not primary iodides, are oxidized to carbonyls is a consequence of the relative ease of displacement at primary centers coupled with the relative facility for secondary alcohol oxidation to carbonyls.

The proposed pathways leading to the various products from peracid oxidation of alkyl iodides are summarized in Scheme III. Thus, the iodide **13** is oxidized to the iodosyl compound **14** which may dissociate to ion pair **15**, possibly with subsequent alkyl migration, or **15** may be a step in the proposed iodosyl–hypoiodite rearrangement (**15** → **19**). Nucleophilic attack on **14** (S_N2) or **15** (S_N1) would lead to **18** (an alcohol when water is the nucleophile). Elimination of hypoiodous acid, by either a concerted

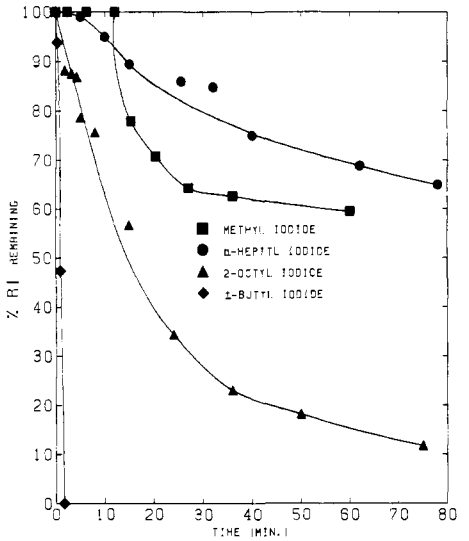
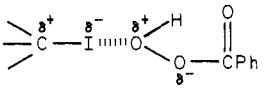


Figure 2. Dependence of the reactivity of alkyl iodides on the nature of alkyl groups. Reaction conditions: RI (0.3 mmol); *m*-CPBA (0.6 mmol) in $CDCl_3$ (10 mL) containing D_2O (0.1 mL) at 0 °C.

syn elimination[6b] or a stepwise pathway involving **15**, would lead to olefin **16** which may be further oxidized under the reaction conditions to epoxide **17**. Ketone **20** arises by oxidation of alcohol **18** and also may be formed from hydrogen iodide elimination from an intermediate alkyl hypoiodite **19**.

The effect of temperature and solvent on the product distribution is secondary to the effect of substrate structure. Oxidation of 2-iodooctane in methylene chloride over a temperature range of 120 °C is summarized in Table I (experiments 7–11). The most obvious trend is the increased oxidation to ketone at higher temperature. The ratio of elimination product **11** to displacement products **9**, **10** and **12** remains essentially constant over the temperature range. The effects of solvent polarity are shown by experiments 12–20. At constant temperature (0 °C) the most obvious trend is increased ketone formation in less polar solvents. The amount of ester formed in each solvent varies markedly with no particular dependency on solvent polarity. This difference could be simply a function of water availability in the various solvents.

The overall rate of peracid-mediated conversion of alkyl iodides to products is dependent upon the alkyl group (Figure 2). The rate of alkyl iodide reaction followed the order: *tert*-butyl > *sec*-octyl > methyl ≳ *n*-heptyl. If halogen oxidation is the rate-determining step in the formation of observed products (vide infra), this rate ordering could reflect the existence of a polarized transition state for peracid oxidation of the alkyl iodide (e.g., **21**)



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or of a significant shift of electron density away from carbon to iodine as the reaction coordinate progresses from alkyl iodide to alkyliodosyl compound. The latter suggestion is attractive because it also rationalizes the hyperelectrophilicity of these alkyliodosyl species.

Conclusion and Biological Significance. Hypervalent organoiodide species, generated in situ by peracid oxidation, decompose via three major pathways—substitution, elimination, and α-carbon oxidation–depending upon substrate structural parameters and solvent. The transient hypervalent organoiodide species have been established to be potent electrophiles and are suggested to be alkyliodosyl compounds. We propose that alkyliodosyl and analogous hypervalent organochloride and -bromide species (chlorosyl and bromosyl compounds) may be generated via cytochrome P-450 mediated oxidation of alkyl halides in vivo. We have obtained evidence for the involvement of iodosyl species in cytochrome P-450 metabolic processes in vitro. Iodosylbenzene has been utilized as an "active" oxygen source to generate the

catalytically active oxenoid cytochrome P-450 species in the absence of oxygen.[11] We have recently established this process to be reversible—that is, the activated cytochrome P-450 form oxidizes iodobenzene to iodosylbenzene.[12] Thus, the oxidation of alkyl iodides by cytochrome P-450 could lead to alkyl iodosyl species as transient, reactive metabolites. That analogous hypervalent organochloride and -bromide species (chlorosyl and bromosyl compounds) could be generated via cytochrome P-450 mediated oxidation and not peracid oxidation is a consequence of the substantial difference in oxidation potential between the two oxidants.[2d,13] Oxidation of alkyl chloride and bromide compounds to their corresponding hypervalent oxidation states via alternate chemical oxidants[18] or electrochemical methods[19] is well established.[20] In the chemical reactions of alkyl halides with oxidants or electrophiles,[7,18] it has been shown that the attacking agent first forms a complex with the halide in many cases and that this complex then breaks up heterolytically to yield products, the overall reaction being abstraction of the halogen: $E^+ + RX \rightarrow [RXE]^+ \rightarrow R^+ + XE$. The metabolism of alkyl halides could exhibit an analogous behavior with the enzymic oxene species as the electrophilic attacking agent.

The chemistry of hypervalent organohalogen intermediates as illustrated here by proposed alkyliodosyl species is compatible with observed biotransformations of halogen-containing organic compounds. The proposition that metabolism of organohalides may proceed by initial halogen oxidation *not* α-carbon oxidation or carbon–halogen bond reduction resolves several unclarified points concerning cytochrome P-450 mediated xenobiotic biotransformations. For example, the rate of metabolic transformation for a series of analogous carbon–halogen-bonded compounds normally follows the order: C–Cl < C–Br < C–I. This order has been rationalized by noting that the ease of carbon–halogen bond reduction increases along this series as a consequence of the decreasing bond dissociation energies for the corresponding carbon–halogen bonds.[21] However, this rationale is not consistent with the observation that many of the products of microsomal or cytochrome P-450 mediated metabolism of compounds which follow this "halide order" appear not to be derived from metabolic reduction. Indeed, products from the oxidative metabolism of alkyl halides by cytochrome P-450 often do not possess altered carbon oxidation states. Formal hydrolysis or dehydrohalogenation processes appear in many instances to rationalize the major metabolic products [e.g., tetrahalomethanes → carbon dioxide;[21] 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) → 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) and/or bis(*p*-chlorophenyl)acetic acid (DDA)].[22] The formation of such products is consistent with intermediate hypervalent halide species since substitution by water (formal hydrolysis) and elimination (formal dehydrohalogenation) are the major reaction processes observed for hypervalent organohalides. The mode of decomposition of the intermediate hypervalent species would be a consequence of the constituency of the enzyme cavity of the particular cytochrome P-450.[2d]

We suggest that mixed-function oxidase-mediated halogen oxidation of organohalides is a major metabolic process. We are currently examining the extent of this process through the correlation of hypervalent organohalide chemistry with in vitro microsomally mediated oxidation of halogen-containing xenobiotic substances.

Experimental Section

General Data. Proton magnetic resonance spectra were recorded at 100 MHz with a JEOL MH-100 spectrometer by using tetramethylsilane as an internal standard. ^{13}C magnetic resonance spectra were recorded at 22.50 MHz by employing a JEOL FX-90Q Fourier transform spectrometer with deuteriochloroform (77 ppm) as internal standard. Low-resolution mass spectra were obtained by GC methods with a Finnigan Series 3200 F quadrapole GC–MS. Infrared spectra were recorded by using a Perkin-Elmer 621 grating spectrometer. Product percentages were determined on the crude reaction mixture by using a Varian 940 FID chromatograph with a 5 ft × $^1/_8$ in. 10% FFAP on Chrom W column between 80 and 220 °C and are reproducible within ±3%. Constant temperature control for reactions between 0 and −60 °C was obtained through use of a Haake EK-51 isothermal bath. The amount of iodine formed in the reaction of *n*-heptyl iodide with *m*-chloroperoxybenzoic acid was estimated by using a Bausch and Lomb Spectronic 20 colorimeter at a wavelength of 505 nm. Some reactions were carried out under an atmosphere of nitrogen, and it was later verified that the product distribution ratio remained unaltered without the maintainence of nitrogen atmosphere. Magnesium sulfate was used throughout as drying agent. (±)-2-Octyl iodide and 1,2-dichloro-3-iodopropene were prepared by the nucleophilic displacement of the corresponding tosylate and chloride, respectively, by iodide ion in acetone.[23] 1,2,3-Trichloropropene was obtained by the elimination of hydrogen chloride[24] from 1,2,2,3-tetrachloropropane (Columbia Organic Chemicals). Cyclohexyl iodide was synthesized by a known procedure.[25] *n*-Heptyl iodide and *m*-chloroperoxybenzoic acid were purchased from Aldrich Chemical Co. *tert*-Butyl and neopentyl iodides were bought from Fluka A-G and were used without purification. Fischer anhydrous ether was used as such whereas Fischer methylene chloride and chloroform were stored over molecular sieves (4 Å) before use. Benzene, from Fischer, was used after distilling the first portion containing water–benzene azeotrope. Fischer tetrahydrofuran was distilled from benzophenone ketyl radical prior to use.

General Reaction of *m*-Chloroperoxybenzoic Acid (*m*-CPBA) with Alkyl Iodides (Refer to Table I). To a solution of *m*-CPBA (1.20 mmol) in the appropriate solvent (25 mL) was added the alkyl iodide (0.60 mmol) via syringe (0.5 min). After the specified time, the reaction mixture was diluted with ether (50 mL) and washed subsequently with aqueous sodium thiosulfate (5% solution, 15 mL, 2 washings), with saturated aqueous sodium bicarbonate (20 mL, 2 washings), and finally with saturated brine solution (15 mL). The organic layer was then dried and the solvent removed in vacuo, affording the crude product mixture. For each of the iodides, a reaction mixture was analyzed, before workup,

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(13) The thermodynamic feasibility of halogen oxide ($RX^+–O^-$) bond formation by the proposed enzymic oxenoid oxygen-transfer process can be shown by examination of the bond dissociation energies for stable analogues of these species. The bond dissociation energies for Cl–O [D(O–ClOH) = 48 ± 3 kcal/mol[14a]], Br–O [D(O–Br–OH) = 46 ± 3 kcal/mol[15]] and I–O [D(O–IOH) = 45 ± 3 kcal/mol[15]] are in the range of known oxenoid heteroatom oxidations executed by cytochrome P-450.[16] The chlorine oxygen bond of such proposed species ($RCl^+ \rightarrow O^-$) was recently calculated by ab initio methods to be stable.[17]

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(16) For example, cytochrome P-450 enzymes are known[2d] to catalyze the conversion of amines into amine oxides [D(N–O) = 47 kcal/mol[15]] and of sulfides into sulfoxides [D(S–O) = 86 ± 2 kcal/mol[14b]].

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(20) We have recently established that alkyl bromides undergo reaction processes consistent with the formation of hypervalent organobromide intermediates upon treatment with oxenoid mimics[5] of cytochrome P-450. These preliminary studies have not ruled out alternate oxidized organobromide species (e.g., cation radicals) and will be reported in due course.

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by ^1H NMR and CMR spectroscopy. These spectra were compared with those of authentic products.

Isolation and Characterization of Iodine Pentoxide. To a solution of *m*-CPBA (12 mmol) in methylene chloride (60 mL) was added *n*-heptyl iodide (1.3791 g, 6 mmol) via syringe (1.0 min) at room temperature (27 ± 2 °C). After 6 min, the reaction mixture was diluted with petroleum ether (60 mL) and cooled to −40 °C (30 min) and later filtered through a Buchner funnel, using Whatman 50 filter paper. The residue was washed repeatedly with ether until all the *m*-chlorobenzoic acid was removed (test with litmus paper). The remaining white solid was isolated, and the following physical, spectral, and chemical characteristics were determined.

The solid decomposed at temperatures >300 °C while we attempted to determine its melting point [cf. I_2O_5 (Alfa-Ventron) >300 °C, d]. An IR spectrum of the residue (KBr pellet) was in all respects identical with that of authentic I_2O_5 (Alfa-Ventron). The oxidation equivalent of the residue was calculated by iodometric titrations against standard thiosulfate. A value of 27.24 g was obtained as the oxidation equivalent (theoretical 27.83 g).

Determination of the Stoichiometry of the M-CPBA–*n*-Heptyl Iodide Reaction. To a solution of *m*-CPBA (12 mmol) in methylene chloride (100 mL, plus 0.2 mL of water) was added *n*-heptyl iodide (6 mmol) via syringe (1.0 min) at room temperature (27 ± 2 °C). After 6 min, an aliquot (50 μL) of the reaction mixture was withdrawn and suitably diluted with methylene chloride and the iodine content was estimated by colorimetry (67 ± 2% based on RI). At the same time, another aliquot (5 mL) was withdrawn and analyzed for its total oxidation equivalent (65 ± 3% based on initial amount of *m*-CPBA used) by standard thiosulfate titration.

The same experiment was repeated with 1.5 and 4 equiv of *m*-CPBA.

Determination of Kinetics (Figures 1 and 2). To a solution of *m*-CPBA (0.6 mmol) in deuterated chloroform (10 mL) containing D_2O (0.1 mL) at 0 °C was added the alkyl iodide (0.3 mmol) via syringe (2 s). At time intervals, an aliquot (0.2 mL) of the reaction mixture was withdrawn and quenched by adding to a solution (0.2 mL) of sulfur dioxide in $CDCl_3$ at 0 °C in an NMR tube. These samples were analyzed via NMR spectroscopy. The relative amounts of alkyl iodide remaining were then calculated and plotted against time, giving Figure 2.

To a solution of *m*-CPBA (3.0 mmol) in deuterated chloroform (50 mL) at 0 °C was added *n*-heptyl iodide (1.5 mmol) via syringe (2 s). At various time intervals, an aliquot (2 mL) of the reaction mixture was withdrawn into a solution of glacial acetic acid (10 mL) and freshly prepared potassium iodide solution (10% solution, 10 mL) and titrated against standard sodium thiosulfate solution (0.024 N), using starch as indicator. At different time intervals, an aliquot (50 μL) of the reaction mixture was withdrawn and diluted with chloroform (5 mL) and the iodine content estimated by colorimetry (500 nm). NMR spectra were recorded from samples withdrawn during the reaction period (refer to experimental procedure in the previous paragraph) and the relative amounts of alcohol determined via integration. These data were plotted as a function of the percentage of the maximum value obtained for alcohol and iodine formation and the disappearance of the total oxidation equivalent (Figure 1).

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Photostimulated Nucleophilic Aromatic Substitution for Halides with Carbon Nucleophiles. Preparative and Mechanistic Aspects[1]

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Abstract: The photo-$S_{RN}1$ reaction operates efficiently with enolate anions derived from simple ketones and esters, but 2-lithio-1,3-dithiane gives low yields. The sluggish and inefficient reaction of dialkyl-substituted ketone and ester enolates is traced to hydrogen atom transfer from the carbon adjacent to the enolate anion to the transient phenyl radical. The first systematic survey of intramolecular coupling of ketone enolate anions shows that six-, seven-, eight-, and ten-membered rings can be formed, although the β-hydrogen transfer becomes important in certain cases.

That radicals can be trapped by nucleophiles is a widely observed phenomenon. The reactions of *p*-nitrobenzylic halides with nucleophiles are known to involve the trapping of benzylic radicals by the nucleophile in a radical chain process.[4] The nucleophile is thought to initiate the chain reaction by transfer of one electron to the aromatic compound. Prior formation of a charge-transfer complex between the nucleophile and the electron-poor arene may be involved since light of relatively long wavelength can initiate certain reactions; quantum yields in excess of 100 are found.[5]

Bunnett and Kim discovered that unactivated aryl halides are attacked by amide ion in liquid ammonia and proposed a radical chain mechanism initiated by one-electron cleavage of the aryl halide; the pathway is labeled $S_{RN}1$.[6] The observations that light can replace solvated electrons as initiator, that acetone enolate anion and other carbanions can serve as the nucleophile, and that heteroatoms other than halogen can be displaced suggest broad application in attachment of carbon units to aromatic rings.[7]

A radical chain mechanism was proposed by Bunnett as presented in Scheme I.[8] When solvated electrons are employed

Scheme I

$$\text{electron source} + \text{PhX} \xrightarrow{h\nu} [\text{PhX}]^{-\cdot} + \text{residue} \quad (1)$$

$$[\text{PhX}]^{-\cdot} \rightarrow \text{Ph}\cdot + \text{X}^- \quad (2)$$

$$\text{Ph}\cdot + \text{R}^- \rightarrow [\text{Ph–R}]^{-\cdot} \quad (3)$$

$$[\text{Ph–R}]^{-\cdot} + \text{PhX} \rightarrow [\text{Ph–X}]^{-\cdot} + \text{Ph–R} \quad (4)$$

(1) Taken from the Ph.D. thesis of Thomas M. Bargar, Cornell University, 1978. Partially published in preliminary form in *J. Org. Chem.*, **42**, 1481 (1977).

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